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LETTERS

New preparation of stereodefined α,α-unsaturated ketones by carbomagnesiation of α-allenyl ketones

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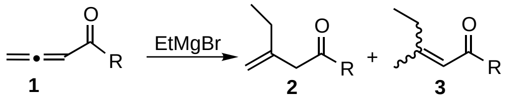
Abstract—The addition of several alkylmagnesium halides to an α-allenyl ketone leads to the corresponding α,β-unsaturated ketones as single geometrical isomers. A π-chelation between the metal and the unsaturation is proposed to explain the steric outcome of this reaction. © 2002 Published by Elsevier Science Ltd.

In the course of our study on the preparation of polysubstituted olefins as single isomers via a carbometalation reaction,[1] we became interested in the reaction of α-allenyl ketones with organomagnesium derivatives. The addition of alkyl magnesium bromide to α-allenyl ketones **1** was originally reported by Bertrand et al.[2] at the beginning of the 1960s and was described to proceed the 1,4-addition of the organometallic to the activated carbon–carbon double bond (namely at the central carbon of the allenyl system). After hydrolysis, the β,γ- and α,β-unsaturated isomers **2** and **3**, respectively, were formed in variable ratios as shown in Scheme 1.

The presence of the α,β-unsaturated ketone **3** was rationalized by the isomerization of the double bond of the non-conjugated isomer **2** into the most stable isomer **3** during the aqueous work-up and the purification step. Moreover, no information on the stereochemistry of the double bond of **3** was described in the original work.[2] When the α-allenyl ketone **1** was treated with lithium dialkylcuprate, variable proportions of unconjugated **2** and conjugated **3** adducts were also formed (in a 30:70 to 90:10 ratio according to the experimental conditions), which were rationalized by the presence of two possible copper complexed intermediates in equilibrium (C-metallated and *O*-metallated).[3] In a similar manner, the addition of lithium dimethyl cuprate to an unisolated steroidal α-allenyl ketone gave the unconjugated ene-ketone.[4] In this Letter, we would like to report that α-allenyl ketone **1a** reacts smoothly under mild conditions with organomagnesium compounds in Et_2O to give, after hydrolysis, only the α,β-unsaturated ketone derivative **3** as single stereoisomer, in contrast to the previous reports. Allenyl ketone **1a** (R = Bu) was easily prepared by a Dess–Martin oxidation (DMP)[5] of homopropargylic alcohol **4a** followed by purification of the crude reaction mixture by column chromatography on silica gel. Under these conditions, terminal propargyl ketones are isomerized into the corresponding α-allenyl ketones in quantitative yields.[6] When **1a** was treated with Grignard reagents at −78°C, followed by hydrolysis at low temperature, the corresponding α,β–unsaturated ketones **5**–**9** were obtained in good yields as described in Scheme 2. The scope of the reaction is broad since primary, secondary and even tertiary alkyl magnesium bromide derivatives react cleanly with the allenyl ketone **1a**. Only phenylmagnesium bromide gave a low yield since a small amount of the 1,2-adduct was formed (direct addition to the ketone) to give the phenyl allenyl carbinols. In all cases, only the *E*-isomer was formed. We believe that this unique stereoselectivity in the formation of the α,β-unsaturated enones **5**–**9** cannot be the result of the isomerization of the non-conjugated enones into the conjugated enones (i.e. the difference between the two geometrical isomers of **5** is too small to explain the formation of a unique product) but must be due to the stereochemical outcome of the hydrolysis of the dienolate anion.[7]



Scheme 1.

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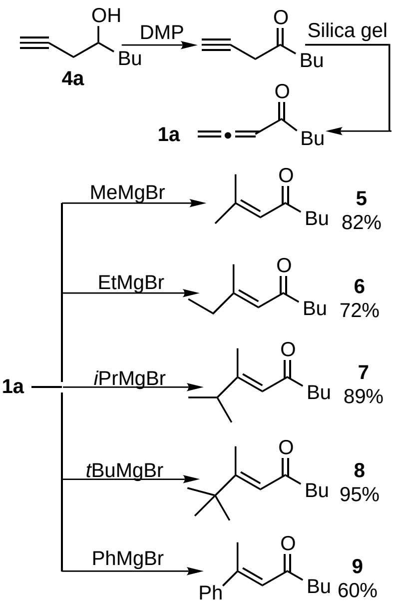
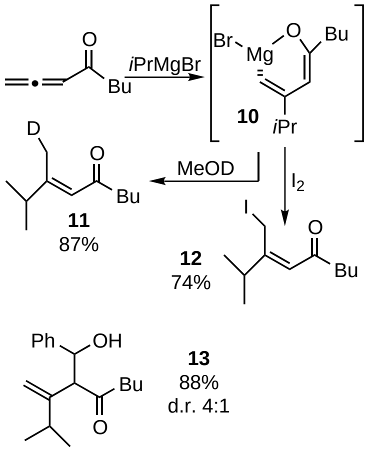


Scheme 2.

In order to gain more insight into the mechanism, we trapped the intermediate **10** at low temperature by the addition of MeOD and iodine to give **11** and **12** as single geometrical isomers (Scheme 3). This unique stereoselectivity result is most probably due to the π-chelation of the magnesium enolate with the terminal double bond.[8] In this case, a dipolar interaction between $Mg^{+\delta}$–$O^{-\delta}$ and the sp^2 carbon is postulated and leads to the cyclic intermediate **10**. Then, by addition of the electrophile, reaction occurs at the terminal position leading to the expected products. In order to assess this hypothesis, we considered that using a solvent that coordinates to the magnesium atom more efficiently than ether, would override the π-electron donation of the double bond. We thus compared the reactions in Et_2O and THF. In ether, a single isomer was formed (Scheme 2) whereas in THF the ratio of **2**:**3** was now 33:66. This result can be interpreted as a result of the weakening π-chelation favoring solvation of the metal by a more electron donating solvent. Similarly, when an aldehyde is added as the electrophile, the chelation between the magnesium enolate and the carbonyl moiety of the electrophile is stronger than the chelation between the magnesium and the double bond. In this case, the aldolization reaction occurs via a chair-like transition state to give exclusively the homoallylic aldol product **13** in good yield but in a modest diastereomeric ratio. In conclusion, the reaction between the organomagnesium halide and the allenyl ketone has been reinvestigated and was found to give only the α,β-unsaturated ketone as single geometrical isomer.



Scheme 3.

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